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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,228	07/03/2003	Arthur M. Krieg	C1037.70045US00	4680

23628 7590 10/15/2007
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EXAMINER	
MINNIFIELD, NITA M	
ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
10/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/613,228	KRIEG, ARTHUR M.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *5,13,15,47-51,55,56,64 and 65* is/are withdrawn from consideration.

5)☒ Claim(s) *1-4,8-12,14,16-20,22,27-32,43,45,53,57,70-73,76-80,83,84,88,89,95,97 and 99* is/are allowed.

6)☒ Claim(s) *46,52,54,63 and 94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/11/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-5,8-20,22,27-32,43,45-57,63-65,70-73,76-80,83,84,88,89,94, 95,97 and 99.

DETAILED ACTION

Response to Amendment

1. Applicant's amendment filed June 25, 2007 is acknowledged and has been entered. Claims 6, 7, 21, 23-26, 33-42, 44, 58-62, 66-69, 74, 75, 81, 82, 85-87, 90-93, 96 and 98 have been canceled. Claims 1-5 8-20, 22, 27-32, 43, 45-57, 63-65, 70-73, 76-80, 83, 84, 88, 89, 94, 95, 97 and 99 are pending in the instant application.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. This application contains claims 5, 13, 15, 47-51, 55, 56, 64 and 65 are drawn to an invention and/or species nonelected with traverse in paper filed June 25, 2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. Claims 1-4, 8-12, 14, 16-20, 22, 27-32, 43, 45, 53, 57, 70-73, 76-80, 83, 84, 88, 89, 95, 97 and 99 are allowable.

5. Claims 63 and 94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 63 is vague and indefinite in the recitation of "second therapeutic"; it is not clear what the first therapeutic is. There is no recitation of a "first therapeutic". Regarding claim 94, the phrase "for

example" ("e.g." exempli grata—Latin for "for example") renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

6. Claims 46, 52, 54 and 94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are methods for stimulating an immune response in a subject in need thereof comprising administering to a subject the immunostimulatory nucleic acid (SEQ ID NO: 1) in an amount effective to stimulate an immune response; the subject has or is at risk of developing cancer; the subject has or is at risk of developing an infection. Claim 54 also administers a cancer antigen. Applicants have elected lung cancer.

It is noted that the specification does not enable the instantly claimed invention. None of the examples set forth in the specification disclose the use of the claimed composition, that being a SEQ ID NO: 1 and a cancer antigen with any of the other possible components (cytokines, adjuvants, mucosal adjuvants and anti-cancer agents, etc) for treatment of a cancer in a subject or a subject that is at risk of developing cancer.

The specification discloses the use of SEQ ID NO: 1 (ODN 10106) in *in vitro* assays that indicate that the nucleic acid can activate TLR9, human B cells and B cell proliferation, all *in vitro*. Th1 dominated immune responses were observed and IFN-alpha secretion. The only *in vivo* evidence provided in the

specification is found on page 95, where mice were immunized with ODN 10106 and HBsAg, an immune response was achieved. There is no evidence of *in vivo* use of the claimed composition comprising SEQ ID NO: 1, cancer antigen, with any of the other additional components. The specification does not predict or teach any positive therapeutic benefit (i.e. treating or preventing cancer or immune response) correlated with the administration of the claimed composition in a rodent or non-rodent subject.

The state of the art with regard to cancer is unpredictable. Tumor cells *in vivo* simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes (Ezzell; see also Forni et al; Peterson et al, Schuh; Kelland). Tumors are classified as immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications. Further, it has been an art-recognized experience that for any novel therapy, the transition from the laboratory to the clinic (animal experiments to bedside) is a quantum leap (Chatterjee et al.). Results obtained under controlled conditions and in inbred animals often differ from the clinical response obtained in patients. This applies in particular to strategies based on immune responses. McCluskie et al teaches that T-rich immunostimulatory nucleic acids do not induce an immune response. *In vitro* animal model studies have not correlated well with *in vivo* clinical trial results in patients. Since the therapeutic indices of immunotherapeutic regimens can be species- and model-dependent, it is not clear that reliance in the *in vitro* stimulation of immune cells with the claimed immunostimulatory nucleic acid and the *in vivo* mouse and non-human primate experimental models with CpG containing ODNs

accurately reflects the relative efficacy of the claimed therapeutic strategy based upon *in vitro* stimulation as disclosed in the specification.

Bitton R. J. (Current Opinion in Molecular Therapeutics, 2004, 6/1:17-25) teaches that developing cancer vaccines to treat solid tumors is not an easy task (abstract). Bitton teaches that "immune editing", in part, explains why many cancer vaccines work in animal models but not in a clinical setting (abstract). Bitton describes the various cancer vaccine strategies and evaluates the evidence supporting their efficacy (abstract). Bitton indicates that the final picture with regard to cancer vaccines is confusing and comparison of different vaccine strategies is almost impossible because of the different strategies from different groups. Further, most of the vaccines are still experimental, far from being approved by regulatory authorities and their clinical utility is almost negligible (abstract). Bitton teaches that therapeutic vaccines have proved to have little use in cancer treatment and that in fact in almost every well-designed, well-controlled, randomized phase III trial, they have failed to demonstrate any significant improvement in overall or disease-free survival (p. 17, col. 2; Table 2). "It is clear that most vaccines are indeed effective immunogens, but they do not seem to be effective at triggering anticancer responses. Tumor size reduction, the classic endpoint in clinical development of cytotoxic drugs does not seem to be useful in evaluating cancer vaccines; tumor stabilization might be more valuable. Finally, there is no evidence of improvement in overall survival or disease-free survival. The implementation of well-designed randomized phase III trials is urgently required." (pp. 24-25)

With regard to CpG in the treatment of cancers, Weiner (J. Leukocyte Biology, 2000, 68:455-463) indicates that there is therapeutic potential in cancer

treatment for CpG as an immune adjuvant (Table 1) and that there are a number of scenarios where CpG could be used as a component of cancer immunotherapy, each of these areas is under intensive investigation (p. 458, col. 1). Studies in a tumor model (38C13 murine lymphoma) indicate that CpG was just as effective as CFA at inducing an antigen-specific antibody response (p. 458, col. 2). Weiner teaches that "[P]reliminary studies suggest CpG ODN can be effective in a variety of scenarios when used alone or in combination with other agents. Despite this promise we still do not understand the molecular mechanisms responsible for the immunostimulatory effects of CpG ODN. All CpG ODN are not alike, and more needs to be learned about the heterogeneous responses that occur based on host organism, cell subset, or CpG ODN sequence. Most importantly, we have not yet explored their clinical effects. Further work with CpG ODN in both the laboratory and the clinic is needed before we can know their true promise as investigational immunological and therapeutic agents." (p. 461, col. 1) Ballas et al (J. Immunology, 2001, 167:4878-4886) teaches that the selection of optimal CpG ODN for cancer immunotherapy depends upon a careful analysis of the cellular specificities of various CpG motifs and an understanding of the cellular mechanisms responsible for the antitumor activity in a particular tumor (abstract). Ballas et al teaches that a single CpG ODN cannot be used to treat all cancers and tumors. Although several CpG ODN were active as sole immunotherapeutic agents in two tumor models, different motifs were optimal in each model. CpG ODN 1585 was optimal against B16 melanoma and its effects were dependent on NK cells. CpG ODN 1826 was optimal in a lymphoma model and its effects appeared to require NK (early) and T cells (late). These results illustrate that the potent distinct CpG motifs can be custom-tailored for each desired immune effect

(p. 4878, col. 2; see also p. 4885, col. 1; see also Wooldridge et al, Current Opinion Oncology, 2003, 15:440-445). Agrawal et al (TRENDS in Molecular Medicine, 2002, 8/3:114-120) also teaches that different effects are observed with different CpG ODNs.

It is noted that the specification does not set forth any teaching or guidance to the skilled artisan for practicing the claimed method. The amount of direction or guidance presented in the specification and the absence of working examples is a hindrance to practicing the claimed invention. One skilled in the art would not accept on its face that the specification is representative of success in practicing the claimed method in view of the lack of guidance in the specification and the known unpredictability associated with the ability to predict if the claimed immunostimulatory nucleic acid (SEQ ID NO: 1) can be used in the claimed method of treating cancer in a subject or preventing/protecting a subject at risk of developing cancer. The quantity of experimentation required to practice the invention as claimed would require the de novo determination of accessible target sites, modes of delivery and formulations of the claimed method. Since the specification fails to provide particular guidance for the use of the claimed method and the art teaches that this is not yet possible (i.e. highly unpredictable), it would require undue experimentation to practice the invention as presently claimed.

Further, for the specification to be enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art and the level of skill in the art. The state of the art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention

pertains at the time the application was filed. The specification must be enabling as of the filing date, not evidence provided several years after the date of filing. The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date. (see MPEP 2164.05(a))

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention and the state of the art has been described above. The level of one of ordinary skill is high (PhD level). The art is unpredictable as previously indicated. With regard to factors 6 and 7, the specification does not provide sufficient direction and the working examples do not enable the claimed method. A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

The state of the art and level of unpredictability have been set forth previously and there are no existing working examples. Applicant has asserted that Examples 1 and 2 demonstrates that the claimed composition can stimulate immune responses both in vivo and in vitro. However, the demonstration using a viral antigen does not indicate that the composition would be useful for treatment for cancers. With regard to McCluskie et al 2001, Applicant has asserted that claimed SEQ ID NO: 1 is not taught and is therefore not relevant. However, the claimed sequence is a T-rich immunostimulatory nucleic acid, and the prior art indicates that some of these sequences do induce an immune response and some do not induce an immune response. Therefore, the state of the art is unpredictable.

It is noted that Applicants have asserted that various references and two Phase III clinical studies demonstrate treatment of first-line non-small cell lung cancer when using CpG ODN 7909, which is similar to the claimed nucleic acids. How similar is CpG ODN 7909 to the claimed CpG ODN 10106 (SEQ ID NO: 1)? Is CpG ODN 7909 a T-rich immunostimulatory nucleic acid as the claimed immunostimulatory nucleic acid (SEQ ID NO: 1)? It view of the state of the art teaching that the CpG immunostimulatory nucleic acids vary with regard to their immunostimulatory activity, it is not clear that the claimed immunostimulatory nucleic acid (SEQ ID NO: 1) would function in the same manner as similar CpG (CpG ODN 7909) does in the method of treating or preventing cancer in a subject (animal or human). Although there is much known and defined about the CpG motif and its effectiveness, the art still teaches that each CpG ODN behaves differently, different effects are observed with different CpG ODNs.

The specification provides insufficient guidance to practice the claimed invention. In view of the lack of the predictability of the art to which the invention

pertains and the lack of established clinical protocols for effective cancer therapies and methods of preventing (i.e. administering to a subject at risk of developing a cancer), undue experimentation would be required to practice the claimed invention with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how on effectively practice the claimed invention.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
September 16, 2007